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Enantioselective Hydrophosphonylation of Aromatic Aldehydes Catalyzed by Chiral Titanium Alkoxides

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Abstract: The enantioselective hydrophosphonylation of aromatic aldehydes with silylphosphite (**1**) or diethyl phosphonate (**5a**) assisted by chiral titanium alkoxides as catalyst is examined. Titanium alkoxide (**7**), derived from L-tratrate and $Ti(O\text{-}iPr)_4$, was found to be an effective catalyst and induce modest enantioselectivity in the reaction.

The chiral α-substituted phosphonic acids such as α-hydroxyphosphonic acids and α-aminophosphonic acids have received considerable attention in medicinal and organic chemistry owing to their potential biological activity and unique structural features.[1] The versatility of α-hydroxyphosphonic acids has been proved recently by their stereoselective conversion to α-aminophosphonic acids as well as by their efficacy as bioisosteres for hybrid transition-state inhibitors of proteolytic enzymes such as renin in peptidic frameworks.[2,3] While the formation of phosphorus-carbon bonds by addition of phosphoric nucleophiles to aldehydes is an effective method for the synthesis of racemic α-hydroxyphosphonic acids,[4] few reports on the enantiodifferential variant of the reaction are available.[5] Recently, optically active α-hydroxyphosphonic acids were prepared by application of the stereoselective cleavage of homochiral dioxane acetals with phosphoric nucleophiles[2b] and enzymatic resolution of racemic α-acetoxyphosphonates or α-hydroxyphosphonates.[6] In this paper we report that the chiral titanium alkoxide derived from L-tratrate is an effective catalyst for hydrophosphonylation of aldehydes and induce modest enantioselectivity in the reaction.

The chiral Lewis acids have been recognized as effective catalysts for the enantioface differentiation of aldehydes and a variety of catalytic reaction systems including cycloaddition, alkylation and hydrocyanation reactions have been developed.[7] To the best of our knowledge, however, catalytic enantioselective hydrophosphonylation of aldehydes using chiral Lewis acids, which is potentially useful for asymmetric synthesis of α-hydroxyphosphonic acids, has never been developed.

In order to examine the feasibility and level of asymmetric induction for the formation of phosphorus-carbon bonds through nucleophilic addition to aldehydes by using chiral Lewis acids, hydrophosphonylation of benzaldehyde with silyphosphite (**1**) in the presence of chiral Lewis acids (**2a,b**)[8] was carried out. Two methods were applied to the reactions. In the first the aldehyde was treated with chiral Lewis acid then **1** was added (Method A). In the second **1** was treated with the Lewis acid followed by addition of an aldehyde (Method B). The results are summarized in Table 1. Benzaldehyde was treated with silylphosphite (**1**) in

toluene at 0 °C for 12 h in the presence of a stoichiometric amount of chiral Lewis acid (**2a**)[8] according to Method A to give (*S*)-(-)-α-hydroxyphosphonate (**3**)[9] with low optical purity in 98% yield (Table 1, entry 1). Siloxyadduct (**4**) was not detected in this reaction. When a catalytic amount of **2a** was utilized under the same conditions, **3** was obtained in low yield (30%) accompanied by siloxy adduct (**4**) (25% yield). The optical purity of **3** thus obtained was approximately equal to that observed in the stoichiometric reaction, while sioxyadduct **4** was almost optically inactive (5% *ee*) (Table 1, entry 2).[9] The enantioselectivity was slightly improved when the method B was applied (Table 1, entry 3). The same results were obtained by the reaction using **2b** (Table 1, entry 4). Although the optical yield of **3** was not satisfactory, these results gave some insights into mechanism for enantioselective hydrophosphonylation of aldehydes using chiral titanium reagents.

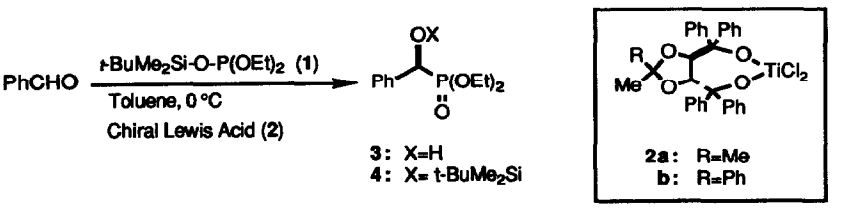


Table 1 Chiral Lewis acid catalyzed reaction of benzaldehyde with **1** [a]

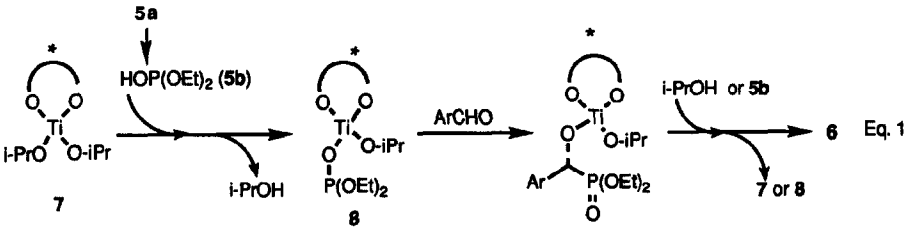
			3		**4**	
Entry	Chiral Lewis acid (mol%)	Method	Yield (%)	Ee(%)[b,c]	Yield(%)	Ee(%)[d]
1	**2a** (100)	A	98	15	0	—
2	**2a** (20)	A	30	17	25	5.0
3	**2a** (20)	B	29	26	24	2.7
4	**2b** (20)	B	31	25	18	0

[a] 1.2 equivalents of silyphosphite (**1**) were used unless stated otherwise. [b] Determined by ^{1}H-NMR (300 MHz) analysis of the corresponding Mosher esters. [c] Specific rotation (in $CHCl_3$) of **3** ranged from -5.6 to -9.6. [d] Determined after converting to **3** [Bu_4NF, THF].

Apparently, the above results show that the formation of **3** and **4** takes place through two pathways: i) transmetalation of **1** with titanium dichloride (**2**) and subsequent addition to an aldehyde to give hydroxy adduct (**3**) which was optically active; ii) activation of an aldehyde with the Lewis acids followed by addition of **1** to give siloxy adduct (**4**) without enantioselectivity. Based on these observations, it was considered that incorporation of the chiral titanium species to phosphoric nucleophile as a template is crucial to an efficient enantioface differentiation of an aldehyde.

Titanium tetraalkoxy derivatives such as **7** would incorporate diethyl phosphonate (**5a**) *via* its phosphite tautomer (**5b**) by exchanging monodentate alkoxy ligand[7b] and under the proper conditions a catalytic cycle would be feasible as shown in Eq. 1. This hypothesis was indeed the case which was proved by the reaction of

benzaldehyde with **5a** using catalytic amount (20 *mol* %) of $Ti(O\text{-}iPr)_4$ in toluene at 0°C to give racemic **3** in 87% yield.[10]



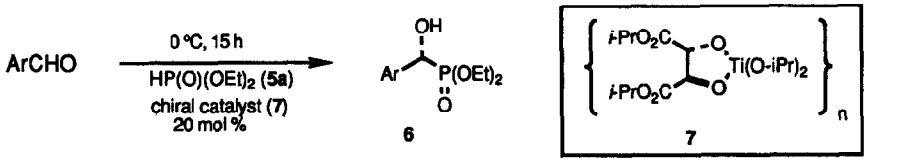


Table 2 Enantioselective addition of diethyl phosphite to aldehydes with the Sharpless catalyst[a]

Entry	Ar	Solvent	Yield(%)	6 Ee(%)[d]	$[\alpha]_D$[e]
1	C_6H_5	Toluene	51	36	+14.0
2	C_6H_5	CH_2Cl_2	12	0	
3	C_6H_5	THF	61	51	+18.2
4	C_6H_5	Et_2O	75[b]	53	+19.1
5	*p*-ClC_6H_4	Et_2O	76[c]	52	+21.9

[a] All reactions were carried out at 0 °C for 15 h in the presence of 20 mol% of the catalyst. [b] mp 74-76 °C. [c] mp 67-70 °C. [d] Determined by ^{1}H-NMR (300 MHz) analysis of the corresponding Mosher esters. Absolute configuration were determined as *R* by comparison of the rotation values with that of **3**. [e] Measured in $CHCl_3$ (c 1.0) at 20 °C.

The Sharpless catalyst (**7**),[11] prepared from diisopropyl L-tartrate and $Ti(O\text{-}iPr)_4$, would be useful as a catalyst for the asymmetric reaction of Eq-1. Lewis acidity of **7** should affect the tautomerization[12] of **5a** to **5b** which is supposed to be crucial for an effective incorporation of the phosphoric nucleophile in the chiral titanium species. The Lewis acidity of **7** could be adjusted for the reaction by the tuning donor or acceptor ability of the solvent used. Then, the reaction of aldehydes with **5a** in the presence of a catalytic amount (20 *mol* %) of **7**[11] prepared *in situ* in several kinds of solvent was carried out (Table 2). Upon treatment of benzaldehyde with **5a**

in toluene, (*R*)-(+)-α-hydroxyphosphonate (**6**) was obtained enantioselectively (36% *ee*) in 51% yield (Table 2, entry 1). When the reaction was conducted in CH_2Cl_2 as the solvent of acceptor ability, no faceselectivity and low chemical yield were observed (Table 2, entry 2). On the contrary, when Et_2O and THF were used as donor solvents, chemical and optical yields of **6** increased to 75% (53% *ee*) and 61% (51% *ee*), respectively (Table 2, entries 3 and 4). The same level of asymmetric induction was observed in the hydrophosphonylation of the aromatic aldehyde having an electron withdrawing chlorine substituent (Table 2, entry 5).[13,14]

Although the enantioselectivity of the present hydrophosphonylation of aromatic aldehydes was modest, this study demonstrated that the acidity of chiral Lewis acid having transition metal such as titanium was important in incorporation of the phosphoric nucleophile as well as differentiation for the enatioface of aldehyde. Further investigations including spectroscopic analysis of the active species are in progress.

References and Notes

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9. Absolute stereochemistry of **3** was confirmed based on its negative cotton effect in CD spectrum[5] and correlation to the authentic sample prepared by our chiral acetal method.[1b] All new compounds gave satisfactory spectoroscopic and analytical data.
10. No reactions occured in the absence of $Ti(O\text{-}iPr)_4$ under the same conditions.
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13. Absolute stereochemistry was determined as *R* by analogous way for **3**.
14. The reaction of anisaldehyde in toluene gave the corresponding adduct in low optical yield (21% *ee*).